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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YEN CHOO and CHRISTOPHER GRAEME ULLMAN

Appeal 2010-001757
Application 09/996,484
Technology Center 1600

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to heterodimeric protein complexes. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R.§ 1.304, or for filing a request for rehearing, as recited in 37 CF.R.§ 41.52, begins to run from July 2, 2010 shown on the PTOL-90A cover letter attached to this decision.

Statement of the Case

Claims 34 and 38 are pending and on appeal (App. Br. 2).

Claims 34 and 38 are read as follows:

34. A complex comprising:
(a) a heterodimer comprising
(i) a first polypeptide, and
(ii) a second polypeptide; and
(b) a ligand that binds to the first and second polypeptides and mediates heterodimerization of the first and second polypeptides,
wherein the first and second polypeptides bind to DNA, and further wherein the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain.

48. A switching system comprising a protein switch comprising: (i) a first component comprising a first polypeptide and (ii) a second component comprising a second polypeptide, in which the first polypeptide binds to the second polypeptide, wherein binding of the first polypeptide to the second polypeptide forms a heterodimer and the binding of the first and second polypeptides is mediated by binding of a ligand to the first and second polypeptides, and (iii) a third component comprising the ligand, wherein the first and second polypeptides bind to DNA, and further wherein the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain.

The prior art

Gilman et al. WO 96/06166 A1 Feb. 29, 1996

The issue

The Examiner rejected claims 34 and 38 under 35 U.S.C. § 103(a) as obvious over Gilman (Ans. 3-5).

The Examiner finds that "Gilman et al. teaches a complex or switching system comprising first and second proteins and a ligand (i.e., multimerizing agent), wherein the ligand binds to both the first and second polypeptides such that the first and second polypeptides are joined to form a heterodimer" (Ans. 4). The Examiner finds that Gilman "teaches Cys2-His2 zinc finger DNA binding domains as one of a small number of explicitly named classes of DNA binding domains that might be comprised by the composite DNA-binding proteins. In addition, Gilman et al. teaches that the zinc finger DNA-binding domains can be engineered by mutagenesis" (Ans. 4).

Appellants argue that the "pending claims require that the DNA binding domain be non-naturally occurring and, thus, every naturally occurring DNA binding domain sequence is excluded from the scope of the claims" (App. Br. 9). Appellants argue that "Gilman fails to teach or suggest anything about engineered zinc finger proteins in addition to failing to teaching anything about non-naturally occurring Cys2-His2 zinc finger binding domains" (App. Br. 9).

Appellants also argue that "Gilman also fails to teach, suggest or enable complexes as claimed in which heterodimerization of first and second DNA binding domains is mediated by a ligand that binds to the DNA binding domains" (App. Br. 9). Appellants argue that "Gilman also only

exemplifies complexes in which two DNA-binding domains are covalently linked as a fusion protein. See, Examples of Gilman. This is entirely unlike the claimed complexes in which a ligand modulates formation of a heterodimer" (App. Br. 10). Appellants argue that "Gilman does not place the public in possession of ligand-mediated heterodimeric complexes as claimed" (App. Br. 11).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Does the evidence of record support the Examiner's conclusion that Gilman renders obvious a heterodimeric complex of claims 34 and 48?

Findings of Fact (FF)

1. Gilman teaches "the use of composite DNA-binding proteins, in which the component DNA-binding proteins are covalently or non-covalently joined together, to obtain high level constitutive or regulated expression of a target gene" (Gilman 2, ll. 5-8).

2. Gilman teaches "DNA-binding proteins containing two or more heterologous DNA-binding domains which are linked together covalently or through an association mediated by a multimerizing agent" (Gilman 2, ll. 9-12).

3. Gilman teaches that the "composite DNA-binding protein comprises two or more such subunits in a multimerizer-mediated association" (Gilman 3, ll. 4-6).

4. Gilman teaches that the "multimerizer-linked composite DBPs [DNA Binding Proteins] comprise two or more chimeric proteins, each comprising at least one binding site for a multimerizing ligand, at least one

component DBD [DNA Binding Domain] such as mentioned above and described in further detail herein, and one or more optional domains" (Gilman 5, ll. 4-8).

5. Gilman teaches that a:

> A second class is proteins in which the DNA-binding domain is comprised of multiple reiterated modules that cooperate to achieve high- affinity binding of DNA. An example is the C_2H_2 class of zinc-finger proteins, which typically contain a tandem array of from two or three to dozens of zinc- finger modules. Each module contains an alpha-helix capable of contacting a three base-pair stretch of DNA. Typically, at least three zinc-fingers are required for high-affinity DNA binding. Therefore, one or two zinc-fingers constitute a low-affinity DNA-binding domain with suitable properties for use as a component in this invention. Examples of proteins of the C_2H_2 class include TFIIIA, Zif268, Gli, and SRE-ZBP.

(Gilman 5, ll. 27-36).

6. Gilman teaches that an "additional strategy for obtaining component DNA-binding domains with properties suitable for this invention is to modify an existing DNA-binding domain to reduce its affinity for DNA into the appropriate range . . . domains that amenable to this type of manipulation include the . . . zinc-finger class represented by steroid hormone receptors" (Gilman 6, ll. 12-28).

7. Gilman teaches that "[m]ultimerizing ligands useful in practicing this invention are multivalent, i.e., capable of binding to, and thus multimerizing, two or more of the chimeric protein molecules. The multimerizing ligand may bind to the chimeras containing such ligand-binding domains, in either order or simultaneously" (Gilman 8, ll. 9-13).

8. Gilman teaches that:

> Individual component DNA-binding domains may be further modified by mutagenesis to decrease, increase, or change the recognition specificity of DNA binding. These modifications could be achieved by rational design of substitutions in positions known to contribute to DNA recognition (often based on homology to related proteins for which explicit structural data are available). For example, in . . . zinc fingers, substitutions can be made at selected positions in the DNA recognition helix. Alternatively, random methods, such as selection from a phage display library could be used to identify altered domains with increased affinity or altered specificity.

(Gilman 10, ll. 4-15).

9. Gilman teaches that "[i]nspection of the structure of related domains may suggest amino acid substitutions that increase binding affinity. Alternatively, a random strategy, such as selection from a phage display library, may be used to select high-affinity protein variants. This strategy is particularly effective with zinc fingers" (Gilman 15, ll. 2-6).

10. Gilman teaches an example which

> involves a pair of chimeric proteins, a dimerizing agent capable of dimerizing the chimeras and a target gene construct to be expressed. The first chimeric protein comprises a composite DNA-binding domain as described herein and a receptor domain (e.g. FKBP) for which a ligand, preferably a high-affinity ligand, is available. The second chimeric protein comprises an activation domain and a second receptor domain (which may be the same or different than on the prior chimeric protein). The dimerizing reagent is capable of binding to the receptor (or "ligand binding") domains present on each of the chimeras and thus

> of dimerizing or oligomerizing the chimeras. DNA molecules encoding and directing the expression of these chimeric proteins are introduced into the cells to be engineered. Also introduced into the cells is a target gene linked to a DNA sequence to which the composite DNA-binding domain is capable of binding. Contacting the engineered cells or their progeny with the oligomerizing reagent leads to regulated activity of the transcription factor and hence to expression of the target gene.

(Gilman 20, ll. 14-29).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

Analysis

Gilman teaches formation of a complex where a "composite DNA-binding protein comprises two or more such subunits in a multimerizer-

mediated association" (Gilman 3, ll. 4-6; FF 3). Gilman teaches that the two or more polypeptides may be non-covalently associated and form a heterodimer with a ligand which mediates the heterodimerization of the two or more polypeptides (FF 1, 2, 4). Gilman specifically teaches that the "multimerizer-linked composite DBPs [DNA Binding Proteins] comprise two or more chimeric proteins, each comprising at least one binding site for a multimerizing ligand, at least one component DBD [DNA Binding Domain]" (Gilman 5, ll. 4-8; FF 4).

Gilman teaches that the polypeptides comprise a Cys2-His2 zinc finger binding domain (FF 5). Gilman teaches that the Cys2-His2 zinc finger binding domain may be engineered by mutagenesis and rational design or by random mutagenesis with phage display (FF 6, 8, 9). Gilman specifically teaches that "[i]nspection of the structure of related domains may suggest amino acid substitutions that increase binding affinity. Alternatively, a random strategy, such as selection from a phage display library, may be used to select high-affinity protein variants. This strategy is particularly effective with zinc fingers" (Gilman 15, ll. 2-6; FF 9).

Gilman teaches an example where the non-covalent multimerized complex is used for regulated gene therapy by binding to a target DNA and impacting gene expression (FF 10).

Applying the *KSR* standard of obviousness to the findings of fact, following the guidance of Gilman to form a heterodimeric complex of two polypeptides which are dimerized by a ligand where at least one of the polypeptides comprises a Cys2-His2 zinc finger which was engineered by mutagenesis represents a combination of known predictable elements which

Gilman would have reasonably expected to function. Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

Appellants argue that the "pending claims require that the DNA binding domain be non-naturally occurring and, thus, every naturally occurring DNA binding domain sequence is excluded from the scope of the claims" (App. Br. 9). Appellants argue that "Gilman fails to teach or suggest anything about engineered zinc finger proteins in addition to failing to teaching anything about non-naturally occurring Cys2-His2 zinc finger binding domains" (App. Br. 9).

We are not persuaded. Gilman expressly teaches that the "[i]nspection of the structure of related domains may suggest amino acid substitutions that increase binding affinity. Alternatively, a random strategy, such as selection from a phage display library, may be used to select high-affinity protein variants. This strategy is particularly effective with zinc fingers" (Gilman 15, ll. 2-6; FF 8-9).

Appellants' argument that Gilman does not teach engineering the fingers is simply incorrect (*see* FF 6, 8-9). Gilman clearly suggests "to modify an existing DNA-binding domain to reduce its affinity for DNA into the appropriate range . . . domains that amenable to this type of manipulation include the . . . zinc-finger class represented by steroid hormone receptors" (Gilman 6, ll. 12-28; FF 6). The only reasonable interpretation of Gilman's teaching to rationally or randomly mutagenize the existing DNA-binding domain of zinc fingers used in the heterodimers is that Gilman is teaching "engineered, non-naturally occurring" zinc fingers (*see* FF 6, 8-9). It is not

reasonable to interpret this teaching as suggesting modifying one "existing DNA-binding domain" which may or may not be naturally occurring into a "naturally occurring" domain.

Appellants also argue that "Gilman also fails to teach, suggest or enable complexes as claimed in which heterodimerization of first and second DNA binding domains is mediated by a ligand that binds to the DNA binding domains" (App. Br. 9). There is no limitation in either Claim 34 or Claim 48 which requires that the ligand which mediates heterodimerization bind to the DNA binding domain (*see* Claims 34 and 48).

Appellants argue that "Gilman also only exemplifies complexes in which two DNA-binding domains are covalently linked as a fusion protein. See, Examples of Gilman. This is entirely unlike the claimed complexes in which a ligand modulates formation of a heterodimer" (App. Br. 10). "[L]imitations are not to be read into the claims from the specification." *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) (*citing In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989)).

We are not persuaded. Gilman provides a specific discussed (though not performed) example in which two DNA-binding domains are linked by a heterodimer and used for gene regulation (*see* FF 10). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971).

Appellants argue that "Gilman does not place the public in possession of ligand-mediated heterodimeric complexes as claimed" (App. Br. 11). However, "proof of efficacy is not required for a prior art reference to be

enabling for purposes of anticipation.... [T]he proper issue is whether the [prior art] is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006). In view of the disclosures referenced above, we agree with the Examiner that Gilman describes the claimed invention such that an ordinary artisan viewing the references' teachings would have been able practice the complex and switching system recited in claims 34 and 48 (FF 1-10). In contrast, Appellants provide no specific evidence that Gilman's description would not have enabled the ordinary artisan to carry out the claimed invention.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Gilman renders obvious a heterodimeric complex of claims 34 and 48.

SUMMARY

In summary, we affirm the rejection of claims 34 and 48 under 35 U.S.C. § 103(a) as obvious over Gilman.

AFFIRMED

dm

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